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Prognostic Value of Dobutamine Stress Technetium-99m-Sestamibi Single-Photon Emission Computed Tomography Myocardial Perfusion Imaging: Stratification of a High-Risk Population

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OBJECTIVES This work was undertaken to define the intrinsic cardiac risk of the patient population referred for dobutamine stress perfusion imaging and to determine whether dobutamine technetium-99m (^{99m}Tc)-sestamibi single-photon emission computed tomography (SPECT) imaging is capable of risk stratification in this population.

BACKGROUND In animal models, dobutamine attenuates the myocardial uptake of ^{99m}Tc-sestamibi resulting in underestimation of coronary stenoses. Therefore, we hypothesized that the prognostic value of dobutamine stress ^{99m}Tc-sestamibi SPECT myocardial perfusion imaging might be impaired, owing to reduced detection of coronary stenoses.

METHODS We reviewed the clinical outcome of 308 patients (166 women, 142 men) who underwent dobutamine stress SPECT ^{99m}Tc-sestamibi imaging at our institution from September 1992 through December 1996.

RESULTS During an average follow-up of 1.9 ± 1.1 years, there were 33 hard cardiac events (18 myocardial infarctions [MI] and 15 cardiac deaths) corresponding to an annual cardiac event rate of 5.8%/year, which is significantly higher than the event rate for patients referred for exercise SPECT imaging at our institution (2.2%/year). Event rates were higher after an abnormal dobutamine ^{99m}Tc-sestamibi SPECT study (10.0%/year) than after a normal study (2.3%/year) ($p < 0.01$), even after adjusting for clinical variables. In the subgroup ($n = 29$) with dobutamine-induced ST-segment depression and abnormal SPECT imaging, the prognosis was poor, with annual cardiac death and nonfatal MI rates of 7.9% and 13.2%, respectively.

CONCLUSIONS Patients referred for dobutamine perfusion imaging are a high-risk population, and dobutamine stress ^{99m}Tc-sestamibi SPECT imaging is capable of risk stratification in these patients. (J Am Coll Cardiol 2001;38:1511–7) © 2001 by the American College of Cardiology

The prognostic value of technetium-99m (^{99m}Tc)-sestamibi single-photon emission computed tomography (SPECT) myocardial perfusion imaging has been firmly established, although most studies to date have employed exercise (1–8) or vasodilator stressors (7–11). For patients with contraindications to exercise and vasodilator stressors, dobutamine stress is frequently substituted under the assumption that the prognostic value of dobutamine ^{99m}Tc-sestamibi SPECT imaging should be comparable. However, there are no studies addressing the prognostic value of dobutamine ^{99m}Tc-sestamibi SPECT imaging in this highly selected patient population. All of the available studies employed liberal criteria for the use of dobutamine and, therefore, included many patients who would have been eligible for exercise (12) or vasodilator stress (13,14).

In the canine model of coronary artery stenosis, dobutamine stress attenuates the myocardial uptake of ^{99m}Tc-sestamibi (15,16), resulting in a significant underestimation of the dobutamine-induced myocardial blood flow heterogeneity on ^{99m}Tc-sestamibi perfusion images. In light of these findings, we hypothesized that the prognostic value of dobutamine ^{99m}Tc-sestamibi SPECT imaging might be inferior to that of exercise and vasodilator stressors, owing to reduced detection of coronary artery stenoses.

Therefore, the objectives of this study were to define the intrinsic cardiac risk of the patient population referred for dobutamine perfusion imaging and to determine whether dobutamine ^{99m}Tc-sestamibi SPECT imaging is capable of risk stratification in this population.

METHODS

Patient population. Between September 1992 and December 1996, 359 consecutive patients were referred to the

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Abbreviations and Acronyms

CAD	=	coronary artery disease
ECG	=	electrocardiogram
MI	=	myocardial infarction
SPECT	=	single-photon emission computed tomography/tomographic
^{99m}Tc	=	technetium-99m
%MAPHR	=	percentage of maximum age-predicted heart rate

University of Virginia for dobutamine myocardial perfusion imaging. Forty-one patients were excluded from this study because planar imaging was employed with ^{99m}Tc-sestamibi (n = 37) or thallium-201 (n = 14). The remaining 308 patients who underwent dobutamine ^{99m}Tc-sestamibi SPECT imaging comprised the study population (Table 1). We reserve dobutamine stress for patients who have contraindications to both treadmill exercise and vasodilator stress agents (obstructive lung disease and/or recent use of methylxanthines). Compared with patients referred for exercise ^{99m}Tc-sestamibi SPECT imaging at our institution (1), patients referred for dobutamine stress were significantly older (62 ± 11 years vs. 58 ± 12 years, $p < 0.001$), more obese (194 ± 50 lbs vs. 181 ± 39 lbs, $p < 0.01$) and shorter in height (66 ± 4 in vs. 67 ± 4 in, $p < 0.01$). The prevalence of prior myocardial infarction (MI) (31% vs. 27%) and female gender (54% vs. 50%) was comparable in patients referred for dobutamine and exercise, respectively (1).

Dobutamine stress protocol. The dobutamine stress variables are summarized in Table 2. Dobutamine was infused in 3-min increments of 5, 10, 20, 30 and 40 μg/kg/min. Atropine was not used to augment heart rate. Chest pain developed during dobutamine infusion in 80 patients (26%), and 52 patients (17%) developed ST-segment depression as defined by standard criteria. Eight patients (3%) developed nonsustained ventricular tachycardia during dobutamine infusion, but no sustained arrhythmias or serious complications were observed.

Table 1. Study Population (n = 308)

	n (%)
Age (yrs)	62 (54, 69)
Women	166 (54)
Obstructive lung disease	241 (79.3)
Theophylline or caffeine use	54 (17.8)
Height (in.)	66.5 (63, 69)
Weight (lbs)	190 (159, 227)
Prior myocardial infarction	93 (31)
Prior surgical revascularization	24 (7.9)
Prior percutaneous revascularization	26 (8.6)
Hypertension	148 (48.7)
Diabetes mellitus	89 (29.3)
Hypercholesterolemia	70 (23.0)
Prior or current tobacco use	150 (49.3)
Beta-blockers	27 (8.9)
Calcium antagonists	88 (28.9)
Angiotensin-converting enzyme inhibitors	79 (26.0)
Nitrates	79 (26.0)

Continuous parameters (age, height and weight) are expressed as median (1st quartile, 3rd quartile). Due to missing data, not all percentages reflect a denominator of 308 patients.

Table 2. Dobutamine Stress Variables

	Median (1st Quartile, 3rd Quartile)
Baseline systolic arterial pressure (mm Hg)	140 (128, 160)
Peak systolic arterial pressure (mm Hg)	160 (140, 178)
Peak heart rate (beats/min)	124.5 (112, 135)
Peak %MAPHR	81 (71, 87)
Peak rate pressure product (× 1,000)	19.4 (16.7, 22.6)
Peak dobutamine dose (μg/kg/min)	40 (30, 40)
Dobutamine-induced side effects	n (%)
Chest pain	80 (26.3)
Dyspnea	29 (9.5)
Nausea	17 (5.6)
Headache	11 (3.6)
Atrial premature beats	66 (21.7)
Ventricular premature beats	150 (49.3)
Nonsustained ventricular tachycardia	8 (2.6)
ST depression > 1 mm	52 (17.1)

%MAPHR = percent of maximum age-predicted heart rate (220 − age); rate pressure product = the product of heart rate (beats/min) and systolic arterial pressure (mm Hg).

Myocardial perfusion imaging protocol. In 98% of patients, a single-day rest-stress ^{99m}Tc-sestamibi imaging protocol was used, with weight-adjusted doses of 8 to 10 mCi of ^{99m}Tc-sestamibi at rest and 25 to 30 mCi at peak stress. In 2% of patients, a separate-day protocol was used, with 25 to 30 mCi ^{99m}Tc-sestamibi for both the rest and stress images. Images were acquired at least 60 min after ^{99m}Tc-sestamibi injection.

Image acquisition and interpretation. Technetium-99m-sestamibi images were acquired using a Prism 3000 triple-headed gamma camera (Picker, Cleveland, Ohio) or a Sophy DS-7 single-headed gamma camera (Sopha Medical, Buc, France). Our methods for image acquisition and quantification have been previously described (17,18). Studies were interpreted clinically by one of five experienced observers using visual and quantitative perfusion data. In 179 patients (58%), the quantitative analysis included an automatic comparison of regional ^{99m}Tc-sestamibi activity to a gender-specific normal database and a quantitative assessment of regional and global left ventricular systolic function using our counts-based gated SPECT method (17,18).

For the purposes of this study, studies were classified as normal or abnormal according to the absence or presence of focal perfusion defects. Studies interpreted as "probably normal" were grouped with the normal studies. Abnormal studies were subclassified according to the presence or absence of perfusion defect reversibility. Studies with "predominantly fixed" (but minimally reversible) perfusion defects were classified as reversible.

Clinical variables. Three clinical variables were prospectively selected as likely predictors of cardiac events based on

Table 3. Follow-Up Events (n [% per year])

	All	Normal	Abnormal
Cardiac events	33 (5.8)	7 (2.3)	26 (10.0)
Cardiac death	15 (2.6)	2 (0.7)	13 (5.0)
Nonfatal myocardial infarction	18 (3.2)	5 (1.6)	13 (5.0)
Surgical revascularization			
Early (≤50 days)	2 (0.4)	0	2 (0.8)
Late (>50 days)	5 (0.9)	0	5 (1.9)
Percutaneous revascularization			
Early (≤50 days)	3 (0.5)	0	3 (1.1)
Late (>50 days)	3 (0.5)	0	3 (1.1)
Noncardiac death	27 (4.8)	18 (5.9)	11 (4.2)

the available literature (1,8). The variables were age, history of prior MI (based on clinical history or diagnostic Q waves on electrocardiogram [ECG]) and number of coronary artery disease (CAD) risk factors (hypertension, diabetes mellitus, dyslipidemia and present or recent tobacco use).

Follow-up. Patients were followed using mailed questionnaires, telephone interviews and review of medical records. Follow-up was terminated at last patient contact or at the time of the following end points: nonfatal MI (confirmed by medical records demonstrating a rise and fall in cardiac-specific markers in the setting of prolonged anginal chest pain and/or ECG changes), cardiac death (sudden death in the absence of other identified causes and confirmed by medical records and/or death certificate), noncardiac death (death from any other cause) or coronary revascularization (percutaneous or surgical). For descriptive purposes, revascularizations occurring ≤50 days after SPECT imaging were classified as "early," and those occurring >50 days after SPECT imaging were classified as "late." All patients who underwent revascularization were censored from subsequent follow-up analysis. Cardiac events were defined as the combined end point of cardiac death or nonfatal MI.

Statistical methods. Event-free survival patterns were analyzed using the Cox proportional hazards regression model for time-to-event data. The Wald chi-square test from this model was used to determine the incremental prognostic value of dobutamine ^{99m}Tc-sestamibi SPECT imaging. Unpaired *t* tests were used to compare demographic data from this study with those reported previously for exercise ^{99m}Tc-sestamibi SPECT imaging in our laboratory (1). Continuous variables are expressed as median (1st quartile, 3rd quartile).

RESULTS

Follow-up events. Follow-up averaged 1.9 ± 1.1 years and was 99% complete. There were 33 cardiac events (15 cardiac deaths and 18 nonfatal MIs) during 566.4 cumulative patient years of follow-up, corresponding to an annual cardiac event rate of 5.8% (Table 3). There were five early revascularizations (three percutaneous, two surgical), all of which occurred in patients with reversible perfusion defects. There were eight late revascularizations (three percutaneous, five surgical). All eight patients had abnormal SPECT studies, and six of eight demonstrated perfusion defect reversibility. Overall, there was a relatively low rate of revascularization (4.2%) and a high rate of noncardiac death (4.8%), reflecting the significant comorbidity of the highly selected study population.

Event rates according to scan results. Figure 1 depicts the event-free survival after dobutamine SPECT imaging, demonstrating significantly greater event-free survival for patients with normal studies (n = 150) than those with abnormal studies (n = 158, $p < 0.001$). The curves begin to diverge early, with few cardiac events during the first year of follow-up in patients with normal studies. In Figure 2, the abnormal studies are segregated according to the presence or

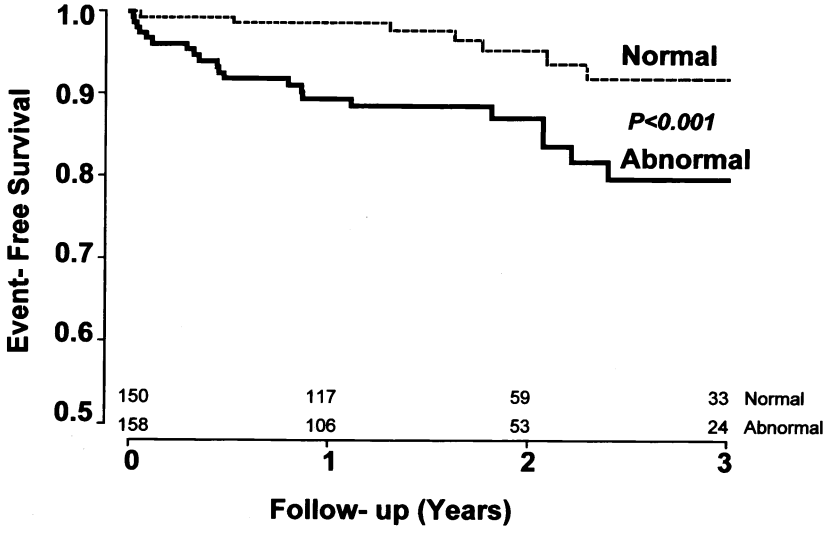

Figure 1. Event-free survival according to the dobutamine technetium-99m-sestamibi single-photon emission computed tomography (SPECT) results. Event-free survival is significantly better in patients with normal SPECT results than it is in those with abnormal SPECT results. The curves begin to diverge early, with relatively few cardiac events during the first year of follow-up in patients with normal SPECT results.

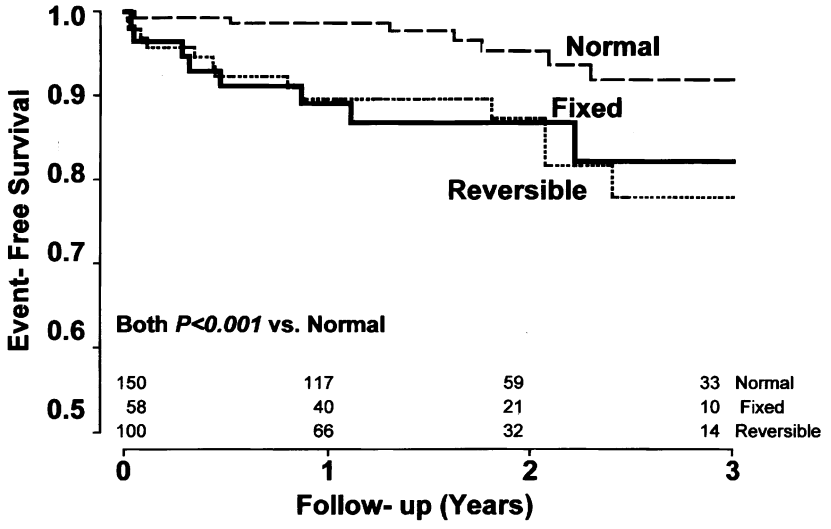

Figure 2. Event-free survival in patients with abnormal single-photon emission computed tomography (SPECT) results segregated according to the presence or absence of perfusion defect reversibility. Although the event-free survival is significantly reduced in both of the abnormal SPECT groups relative to those with normal SPECT results, no significant effect of perfusion defect reversibility was observed on event-free survival.

absence of perfusion defect reversibility. Although event-free survival in both subgroups was significantly reduced relative to that in the normal group ($p < 0.001$), there was no significant difference in event-free survival between those with entirely fixed defects ($n = 58$) and those with at least partial defect reversibility ($n = 100$).

Dobutamine-induced ST-segment depression and cardiac events. Patients with normal ECG responses to dobutamine and normal SPECT imaging ($n = 127$) had a very favorable prognosis ($p = 0.0062$ vs. other groups; Fig. 3), with annual cardiac death and nonfatal MI rates of 0.4% and 1.1%, respectively. In contrast, patients with an abnormal ECG response and abnormal SPECT results ($n = 29$) had a poor prognosis, with annual cardiac death and nonfatal MI rates of 7.9% and 13.2%, respectively. Patients with discordant ECG and SPECT imaging results ($n = 152$) had an intermediate prognosis, with annual cardiac death and nonfatal MI rates of 4.2% and 3.8%, respectively. The proportional hazards model that gave rise to these estimates assumes that the curves for the four groups do not cross. The event-free survival was significantly and independently ($p = 0.22$ for interaction) associated with both ECG ($p = 0.035$) and SPECT ($p = 0.012$) results.

The ECG response and SPECT results were significant independent predictors of cardiac events even after clinical variables (age, history of prior MI and number of CAD risk factors) were considered, as reflected by the Wald chi-square results determined by the Cox proportional hazards

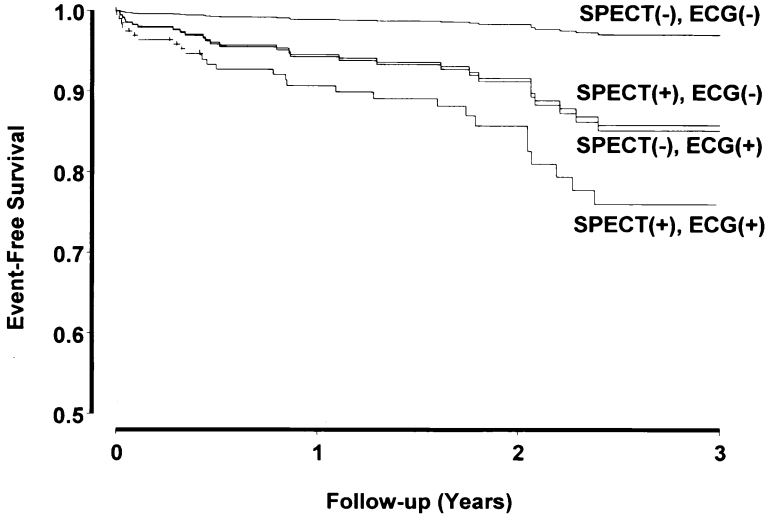

Figure 3. Event-free survival according to the electrocardiogram (ECG) response and the single-photon emission computed tomography (SPECT) results. The event-free survival was significantly and independently associated with both ECG ($p = 0.035$) and SPECT ($p = 0.012$) results. Patients with normal ECG responses and normal SPECT results had a very favorable event-free survival ($p = 0.0062$ vs. other groups). Patients with abnormal ECG responses and abnormal SPECT results had a very high event rate.

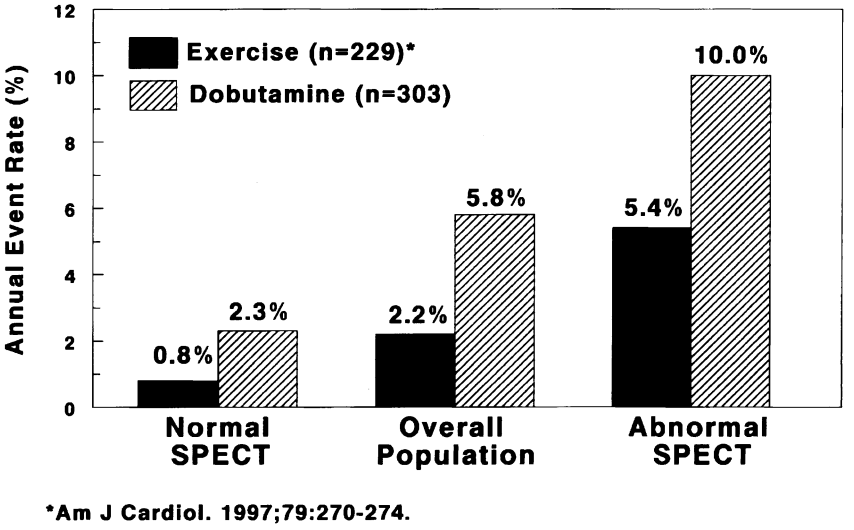

Figure 4. The impact of population risk on the annual cardiac event rates after single-photon emission computed tomography (SPECT) perfusion imaging. Excellent risk stratification is achieved with both exercise and dobutamine SPECT imaging as reflected by a roughly fivefold differential in event rates between patients with normal and abnormal SPECT results. However, regardless of SPECT results, event rates are higher in patients referred for dobutamine stress than they are in those referred for exercise stress, reflecting the higher intrinsic cardiac risk in patients referred for dobutamine perfusion imaging.

model (with and without adjusting for covariables). The ECG response to dobutamine added incremental prognostic information beyond that provided by clinical variables alone ($p = 0.02$). Single-photon emission computed tomography perfusion results add significant incremental prognostic information beyond that provided by the combination of clinical and ECG results ($p = 0.01$).

Failure to achieve target heart rate was not a predictor of cardiac events in our study. The percentage of maximum age-predicted heart rate (%MAPHR) achieved was not a significant predictor of cardiac events ($p = 0.84$), and including %MAPHR in the multivariable model caused no substantive change in the Cox regression coefficients for the ECG and SPECT results as predictors of cardiac events.

DISCUSSION

The major findings of this study were that patients referred for dobutamine stress perfusion imaging are a high-risk population and that dobutamine ^{99m}Tc-sestamibi SPECT imaging is capable of risk stratification in these patients. This study also confirms that the ECG response to dobutamine adds incremental prognostic information, a finding that has not been consistently reported previously. Patients with a normal ECG response and normal dobutamine ^{99m}Tc-sestamibi SPECT perfusion images had an annual cardiac death and nonfatal MI rates of 0.4% and 1.1%, respectively. This was the lowest risk group. In contrast, patients with abnormal ECG responses and abnormal SPECT images had very high rates of cardiac death and MI (7.9% and 13.2%, respectively). Patients with discordant ECG and scan findings (e.g., normal ECG response with abnormal SPECT images) had intermediate event rates. This study also highlights the importance of population risk on the observed annual cardiac event rates after noninvasive testing as discussed in the following text.

Importance of population risk on observed annual cardiac event rates. A major strength of nuclear perfusion imaging is the ability to identify patients at low risk for future cardiac events. In this study, the annual cardiac event rate in patients with normal dobutamine SPECT studies was 2.3%, which is more than twofold higher than the event rates (<1%) reported after a normal exercise SPECT study (1–8). Considered in isolation, this relatively high event rate could be interpreted as clinical confirmation of an adverse effect of dobutamine on myocardial uptake of ^{99m}Tc-sestamibi as predicted in the canine model (15,16). However, cardiac event rates after a normal SPECT perfusion study are determined by two factors: 1) the sensitivity of the test for detecting CAD, and 2) the intrinsic cardiac risk of the population studied. Cardiac event rates will tend to be higher if the test sensitivity is low (patients with "false-negative" results may have subsequent cardiac events) or if the intrinsic cardiac risk of the patient population is high. Therefore, the annual cardiac event rates in patients with normal studies must be interpreted in the context of the overall cardiac risk of the population studied. This is analogous to the well-accepted principle that the predictive values of noninvasive diagnostic testing are dependent on the prevalence of disease in the population examined (19).

This concept is illustrated in Figure 4, which depicts the annual cardiac event rates for patients referred for dobutamine stress (from this study) plotted together with the cardiac event rates in patients referred for exercise SPECT imaging at our institution (1). Excellent risk stratification is achieved with exercise and dobutamine, as reflected by a roughly fivefold differential in cardiac event rates between

patients with normal and abnormal SPECT results (0.8% vs. 5.4% for exercise and 2.3% vs. 10.0% for dobutamine, respectively). However, regardless of the SPECT results, the cardiac event rates are higher in patients referred for dobutamine stress, reflecting the higher intrinsic cardiac risk of the population referred for dobutamine stress (event rate of 5.8% vs. 2.2% for patients referred for exercise). Patients with "abnormal" results on exercise ^{99m}Tc-sestamibi SPECT imaging have a similar annual cardiac event rate (5.4%) to patients who are simply "referred" for dobutamine SPECT imaging (5.8%).

The impact of population risk on annual event rates was also evident in the work of Hachamovitch et al. (8). Event rates were nearly twofold higher in patients referred for adenosine SPECT imaging than they were in patients referred for exercise SPECT imaging, reflecting the higher intrinsic cardiac risk in patients referred for adenosine stress. An imaging test will only provide "risk stratification" (separation of patients into higher and lower risk groups). The absolute cardiac event rates will be determined by the intrinsic cardiac risk of the population.

Comparison with experimental findings in the canine model (prognostic importance of fixed defects). Two independent groups of investigators have recently reported that the myocardial uptake of ^{99m}Tc-sestamibi is attenuated by dobutamine stress in experiments performed using a canine model of coronary artery stenosis (15,16). These experimental findings would suggest that dobutamine ^{99m}Tc-sestamibi SPECT imaging might be relatively insensitive for the detection of mild-to-moderate coronary artery stenoses. At first glance, the excellent risk stratification achieved with dobutamine ^{99m}Tc-sestamibi SPECT imaging in this study might appear to contradict these canine experiments.

However, there are plausible explanations for the apparent discrepancy between the canine experiments and this clinical study. First, in the canine model, a single coronary stenosis is created that reduces flow reserve without reducing resting flow (15), which is clinically analogous to the patient with a moderate single-vessel stenosis without prior MI. In this study, 93 patients (31%) had a history of prior MI. In patients with prior MI, the resting SPECT perfusion image is abnormal; the diagnosis of CAD can be made on the basis of the resting image alone, and the predicted attenuation of ^{99m}Tc-sestamibi uptake by dobutamine stress is "prognostically irrelevant." An underestimation of stress perfusion defect severity (as predicted by the canine experiments) would not alter the correct classification of the study as "abnormal" on the basis of a fixed perfusion defect. In support of this hypothesis, we noted that resting images were abnormal in the majority of patients classified as having abnormal SPECT studies (all patients with fixed defects by definition and 90% of patients with "reversible" defects had at least some degree of associated fixed defect). Secondly, in some cases the stress perfusion defect severity may have been artifactually enhanced by persistent regional myocardial dysfunction during post-stress image acquisition (15,20). Dobutamine-induced myocardial stunning has recently been observed in the canine model (15). Finally, it is possible that the interaction between dobutamine and ^{99m}Tc-sestamibi is unique to the canine species and does not occur in humans, although the canine species has proved to be a reliable predictor of human radionuclide tracer kinetics in the past.

ECG response to dobutamine. Dobutamine-induced ST-segment depression has been reported to have a sensitivity of 18% to 28% for detecting CAD (21–23), a sensitivity that is inferior to that provided by ^{99m}Tc-sestamibi SPECT perfusion imaging or echocardiography during dobutamine stress (22).

However, in this study, the ECG response to dobutamine provided significant incremental prognostic information beyond that provided by standard clinical variables. The prognostic information provided by the ECG response was independent of the SPECT imaging results. Of particular clinical relevance is the finding that a low-risk group could be identified on the basis of a concordantly normal ECG response and normal SPECT result. Further studies are needed to clarify the role of the ECG response to dobutamine in risk assessment and clinical decision making.

Study limitations. Our results should be extrapolated with caution to other laboratories and other patient populations. As mentioned previously, we tend to reserve dobutamine stress for patients with contraindications to exercise and vasodilator stressors. The annual cardiac event rates may differ if dobutamine ^{99m}Tc-sestamibi SPECT imaging is used more liberally, such as in patient populations without contraindications to exercise or vasodilators.

Attenuation correction of SPECT perfusion images was not utilized in our study, and gated SPECT imaging was used in only 58% of patients. It is possible that the prognostic value of dobutamine ^{99m}Tc-sestamibi SPECT could be further enhanced by the routine application of these techniques.

Our relatively small population size prevented analysis of the cardiac event rates in patients with abnormal studies according to the extent and severity of perfusion abnormalities. Larger studies would be necessary to define the impact of perfusion defect extent and severity on event-free survival.

The single-day, rest-stress imaging protocol may have resulted in a slight underestimation of stress perfusion defect severity due to contamination of stress tracer distribution by residual tracer activity from the resting injection. However, despite this theoretic limitation, the rest-stress imaging protocol is widely used, and our results are, therefore, relevant to current clinical practice.

Clinical implications. Despite the theoretic potential for underestimation of coronary stenoses, dobutamine ^{99m}Tc-sestamibi SPECT myocardial perfusion imaging is capable of cardiac risk stratification in high-risk patients with contraindications to exercise and vasodilator stressors.

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